REMARKS

Claims 1-14 are pending in this application. Claims 2-6 have been amended to clarify claim language.

Rejections Under 35 U.S.C. §102

The Examiner maintained the rejection of claims 1-3, 6-10 and 13-14 under 35 U.S.C. §102(e) as anticipated by Mechanic U.S. patent 5,332,475 ("Mechanic '475"). According to the Examiner, "Mechanic (col. 2, lines 42-68; col. 3, lines 1-2 col. 4, lines 19-53) discloses using collagen fibrils or finely ground bovine skin collagen in a cross-linking process not subjected to an acid dissolution to make collagen fiber/fabric/matrix to be used inside a human being as an implant. Inherently, the product to be used inside a human body must have been sterilized."

Applicants have previously amended claims 1 and 8 to overcome the 35 U.S.C. §102 rejection of the claims as being anticipated by Mechanic '475.

Applicants respectfully request that the Examiner withdraw the rejection for the following reasons. The Mechanic '475 patent was cited as the basis for claim rejections during prosecution of the parent application directed to a process for preparing a collagen fiber and products produced thereby (Serial No: 09/209,723; filed: December 11, 1998; "COLLAGEN HEMOSTATIC FIBERS", Robert D. Torgerson et al., now U.S. patent 6,361,551 B1). The parent application involved forming collagen suspensions in water. Applicants successfully overcame the rejections using the Declaration of Stephen Eldridge and related documents presented during prosecution of the aforementioned parent application. Applicants respectfully request that the Examiner reconsider and withdraw the outstanding claim rejections based on the arguments made and the supporting documents presented previously with the Applicants' May 17, 2004 response. Applicants, hereby, reiterate these arguments.

Mechanic '475, discloses an improved method for cross-linking collagen products and the collagen products produced thereby. All of the Mechanic products are produced using a photooxidative dye which acts as a cross-linking oxidation catalyst or promoter (column 3, lines 53-61):

> "The process of the present invention provides cross-linked, stabilized proteinaceous products which are suitable biomaterials for use in the replacement and/or repair of diseased or damaged body tissues (medical prosthetics). When so used, the products of the present invention are superior to products previously employed, for they

> retain the mechanical properties of the pre-treated material, that is, they remain supple and pliant."

The Mechanic '475 products are cross-linked using the disclosed photooxidation process. Mechanic '475 does not teach or suggest lyophilizing a suspension of a proteinaceous substance to form a hemostatic fabric comprising collagen fibrils wherein the fibrils have been suspended in water. In contrast to Mechanic '475, Applicants' invention is directed to the use of collagen fibrils in water for fabricating a collagen fabric with retention of hemostatic activity.

Applicants' claimed invention is based, in part, on Applicants' discovery that acid dissolution of collagen causes irreversible damage to its hemostatic activity. Thus, the invention is directed to methods to form a collagen product and the products produced thereby, which involve suspending collagen in water and avoiding acid dissolution. Although water itself is a pH neutral liquid, collagen fibrils are acidic and, when collagen is suspended in water, the pH of the resulting suspension is in the range of about pH 3.04 to about pH 3.09. Applicants previously submitted the Eldridge Declaration as evidence of the acidic pH that is obtained when collagen fibrils are suspended in water. The pH of a collagen suspension in water is acidic because water does not have buffering capacity.

Mechanic '475 discusses the disadvantages of dispersing collagenous material in aqueous acid solution (Col. 2, lines 42-49):

> ...Acid has the well known effect of denaturing the protein comprising the collagen fibril. It is, of course, the three-dimensional structure of the proteins comprising the collagen fibril which imparts to the fibril the unique properties of collagen; change that structure and the protein cannot interact in the manner needed to give rise to those properties.

Mechanic '475 describes a process for cross-linking and stabilizing proteinaceous material such that the end product of this process retains "*the mechanical* properties of the pre-treated material, that is, they remain supple and pliant" and in addition, the product is "non-immunogenic" (Col. 3, lines 52-61). Mechanic '475 also refers to an object of the invention as being the provision of a product "having *physical-chemical* properties which make that product useful for use as a biomaterial for use an artificial tendon, heart valve, or pericardial patch" (Col. 3, lines 10-11). In order to accomplish this objective, Mechanic '475 teaches that the

proteinaceous material to be cross-linked is immersed in an aqueous media that is suitable for processing in accordance with the Mechanic '475 invention. Mechanic '475 states (beginning at Col. 4, line 50, emphasis added):

> "The proteinaceous material to be photoxidized is then immersed, dispersed, or suspended (depending upon its previous processing) in an *aqueous media* for processing in accordance with the present invention. Suitable media for immersion of the proteinaceous material (for purposes of convenience, the word "immersion" shall be considered to include suspension and/or solubilization of the proteinaceous material) include aqueous and organic buffer solutions having a neutral to alkaline pH, preferably a pH of about 6.5 and above because of the denaturation caused by acid pH. Particularly preferred are buffered aqueous solutions having a pH of from about 6.8 to about 8.6.

Thus, Mechanic '475 teaches that acid dissolution of collagen should be avoided to retain collagen's "mechanical properties" or its "physical-chemical properties". Mechanic '475 also teaches the importance of dispersing proteinaceous material in an aqueous media having a neutral to alkaline pH.

The above quoted passage from Mechanic '475 is directed to preparing suspensions of "proteinaceous materials". However, when one places collagen fibrils in water, the result is a suspension which has an acidic pH. (See Eldridge Declaration – previously submitted -) This is due to the acidic nature of the collagen molecules and the non-buffering capacity of water. Thus, although the Mechanic '475 patent broadly discloses placing proteinaceous material in an aqueous medium that could be water, a suspension of collagen in water would not result in a suspension having a neutral to alkaline pH as set forth in Mechanic '475. There are some proteins which inherently have a neutral pH and, therefore, placing such neutral proteins in water results in an aqueous suspension having a neutral pH; however, collagen is not a neutral protein. Accordingly, the pH of a collagen suspension that is prepared in accordance with Applicants' claimed method of suspending collagen particles in water to form a collagen slurry is acidic.

There are no further teachings in the Mechanic '475 patent to suggest using water to suspend collagen or any other "proteinaceous material". All of the examples in the Mechanic '475 patent involve suspending collagen in aqueous buffered solutions. All of the Mechanic '475 claims require performing the cross-linking step in an aqueous buffer such that the pH is

maintained at between about 6.8 and about 8.6 or in a buffered medium having a neutral to alkaline pH.

Mechanic '475 is a divisional of U.S. Patent No. 5,147,514 ("Mechanic '514"). Although the two Mechanic patents ('475 and '514) identify water in the table of media in Col. 4, neither of the Mechanic patents describes any further use of water to prepare a collagen suspension. Indeed, the Mechanic '514 file history is consistent with Applicants' interpretation of the Mechanic patents as teaching the need for a buffered medium in order to maintain the integrity of collagen fibrils. Thus, all of Mechanic '514 claims require the use of aqueous buffered medium solution having a pH from about 6.8 to about 8.6.

During prosecution of Mechanic '514, the Applicants argued that a pH below neutral (about 7.0) "jeopardizes the integrity of the collagen fibrils" and submitted a Rule 132 Declaration of David Cheung, Ph.D, to support this assertion. A copy of the Cheung Declaration was previously submitted. The Examiner's attention is directed to ¶12 of the Cheung Declaration which describes the necessity for maintaining physiological pH ("i.e., pH=7.4" when collagen is reconstituted; Cheung Declaration ¶12, emphasis added):

> Native collagen fibrils have a specific structure which results from the alignment of the individual collagen molecules comprising the fibril in a helix in such a way that the fibril is referred to as being "quarter-staggered array." ...It is now known that only collagen in the intact, native collagen fibril plays a role as a structural/connective tissue protein and that such fibrils can only be obtained by reconstitution of collagen under precisely controlled conditions, the most important of which is that the reconstitution be performed at physiological pH (i.e., pH=7.4).

In connection with submitting the Cheung Declaration, the Mechanic '514 Applicants argued (response submitted March 14, 1991, pages 6-7, emphasis added – previously submitted with Applicants' May 17, 2004 response):

> ...As will be made clear by the discussion of the affects of acid on collagen fibrils that will be set out in the Cheung Declaration, a pH below neutral (about 7.0) jeopardizes the integrity of the collagen fibrils. Consequently, Applicants' claim 1 recites that the collagen fibrils are soaked in a medium "buffered to a pH of from about 6.8 to about 8.6") e.g., a pH which does not denature the collagen fibrils) for photooxidation. As will be further developed in the

> Cheung Declaration, in the case of the process described in Kuntz [a reference cited against the Mechanic claims], the fibrils were already denatured (e.g., they were not longer fibrils) such that it did not matter whether the irradiation was conducted in acidic pH.

The Mechanic patents and their file histories are public documents which should be considered in their entirety in assessing the Applicants' pending claims. In view of the foregoing, one skilled in the art would consider the Mechanic patents and their file histories and conclude that although Mechanic '475 includes water as an aqueous medium into which proteinaceous material can be dispersed, the Mechanic '475 and '514 file histories further suggest that it is important to place collagen in a buffered medium because "a pH below neutral (about 7.0) jeopardizes the integrity of the collagen fibrils". Water is not a buffered medium; collagen is an acidic protein and consequently, a suspension of collagen in water has a pH of from about pH 3.04 to about pH 3.09 (see Eldridge Declaration – previously submitted) with Applicants' May 17, 2004 response. Because the pH of a collagen suspension in water is acidic (even though acid is not used in Applicants' process, the resulting suspension has an acidic pH), this would be contrary to the Mechanic patent teachings, which emphasize the importance of maintaining collagen at a neutral and avoiding a pH below pH 7.0.

When considered as a whole for all of its teachings, Mechanic '475 teaches only cross-linked collagen fibers and does not teach or suggest suspending collagen in water to form a hemostatic fabric. Accordingly, Mechanic '475 does not anticipate any of the instant pending claims.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims as anticipated by the Mechanic '475 patent.

Rejections Under 35 U.S.C. §103

The examiner maintained the rejection of claims 4-5 and 11-12 under 35 U.S.C. §103(a) as being unpatentable over Mechanic '475.

The arguments presented above in response to the rejection of claims as anticipated by Mechanic '475 are also applicable to the obviousness rejection. When considered as a whole for all of its teachings, Mechanic '475 does not teach or suggest suspending collagen fibrils in water to form a fabric. On the contrary, Mechanic '475 teaches away from suspending collagen fibrils

in water. Moreover, Mechanic '475 teaches only crosslinked collagen fibers. Accordingly, Mechanic '475 does not render obvious any claim which includes a limitation of suspending in water collagen fibrils that are not crosslinked. Moreover, claims 4-5 and 11-12 are dependent upon a base claim (claim 1) which was rejected as anticipated by Mechanic '475. Because Mechanic '475 does not teach or suggest or render obvious the base claim, Mechanic '475 does not render obvious the dependent claims that depend from the base claim.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
***Torgerson et al.**, Applicants*

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